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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,624	10/26/2001	Keith D. Allen	R-666	1008

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DELTAGEN, INC.
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EXAMINER
PARAS JR, PETER

ART UNIT	PAPER NUMBER
1632	12

DATE MAILED: 09/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,624	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *1-4,7-11,39,41 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,6,12-38 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group III, claims 5-6, 12-38 and 40 in Paper No. 11 is acknowledged. The traversal is on the ground(s) that the Examiner has not shown that a serious burden would be required to examine all the claims. This is not found persuasive because each of the Inventions has a different classification and requires a separate search status. It is noted that the classification of Group VII was inadvertently omitted from the Restriction requirement; the classification for Group VI should have been included as follows: Class 530, Subclass 350. In particular, it is maintained that the products of Groups I, II, III, VI and VII are different each from the other; they each have different chemical structures and can be used in materially different methods that require different technical considerations. For example, the DNA targeting construct of Group I can be used to disrupt a TSH-R gene in a somatic cell *in vitro*, cells of Group II can be used to produce a protein, the transgenic non-human animal of Group III can be used as a model of disease, the unknown agents of Group VI can be used for modulating the expression of a TSH-R gene and the agonist or antagonist of Group VII can be used for modulating the function of a TSH-R. It is maintained that the products of Inventions I, II, III, VI and VII are distinct due to their divergent subject matter (DNA targeting construct, isolated cells comprising a disruption in a TSH-R gene, transgenic non-human animal, unknown agent that can modulate the expression of a TSH-R gene, an agonist or antagonist that can modulate the function of a TSH-R) and are separately classified and searched.

It is maintained that the methods of Groups IV and V are distinct, comprising different methodologies and using different products. For example, the method of Group V can be practiced in a somatic cell *in vitro*, while the method of Group IV requires a transgenic non-human animal for practice. It is maintained that the methods of Groups IV and V are distinct as they are directed to different methods that require the use of different products that need different technical considerations (somatic cells *in vitro* and transgenic non-human animals) and are separately searched and classified.

It is maintained that the products of Groups I, II, III, VI and VII are distinct from the methods of Groups IV and V; the products of Groups I, II, III, VI and VII can be used in methods, which require different reagents and technical considerations from the methods of Groups IV and V. For example, the DNA targeting construct of Group I may be used as a probe in a hybridization assay *in vitro* while the transgenic non-human animal of Group III may be used to produce antibodies to an antigen, while the method of Group IV may be used to identify agents that modulate the expression of a TSH-R gene. The method of Group IV may be practiced with agents that have different chemical structures from the agents of Groups VI and VII. It is maintained that the products of Groups I, II, III, VI and VII are distinct from and can be used in different methods (hybridization assays, generating antibodies) from the methods of Groups IV and V.

Therefore it is maintained that all the inventions are distinct each from the other for the reasons given above. The requirement is still deemed proper and is therefore made FINAL.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 1-4, 7-11, 39, and 41-42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

The requirement is still deemed proper and is therefore made FINAL.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached **N**otice To Comply With Requirements For Patent Applications Containing **N**ucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicants are required to comply with all of the requirements of 37 C.F.R. §§ 1.821 through 1.825. *Any* response to this Office Action, which fails to meet all of these

requirements, will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. §§ 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-6, 12-38, and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a homozygous disruption of the nucleotide sequence set forth in SEQ ID NO: 1, wherein the mouse exhibits the following phenotypes: dwarfism; hunched posture; small eyes and ears; small thymus gland; a malformed femur; small skeletal muscle; decreased fat in the subcutis; small or not visible seminal vesicles; low body weight; short body length; low organ weight (spleen, liver, kidneys, heart, thymus); low organ weight to body weight ratio (spleen, liver, kidneys); small thyroid gland with small follicles; abnormalities of the pituitary gland consisting of adenohypophysis, large and vacuolated cells, reduced chromophils, pars distalis, and chromophobe hypertrophy; dysplasia of the epiphyses of the femur, tibia and stifle joint; reduced patchy ossification of bones; reduced cellularity of bone marrow; hypoplasia with absence of cortico-medullary distinction of the thymus gland; immature kidneys with small glomeruli,

lymphocytic infiltrates in the kidneys; immature testes; hypospermatogenesis; insterstitial Leydig cell hyperplasia; oligospermia; lymphocytic infiltrates in the lungs; diffuse retinal fibrosis and elevated blood urea nitrogen; and methods of making the same and using same to screen for agents that might ameliorate a phenotype of the same does not reasonably provide enablement for all other transgenic non-human animals embraced by the claims and methods of making and using the same, The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed transgenic non-human animals, particularly a mouse, that comprise a disruption in a TSH-R gene.

The specification teaches the generation of transgenic mice by disruption of the nucleotide sequence set forth in SEQ ID NO: 1. See page 10, and the working example on pages 55-62 of the specification. The specification teaches that these knockout mice when homozygous for the disruption of the sequence set forth in SEQ ID NO: 1 exhibit the above recited phenotypes. See pages 55-62 of the specification. While the specification has taught the generation of such a homozygous transgenic knockout mouse having, the specification has not taught the generation of the other transgenic non-human animals encompassed by the claims. The working examples, guidance and relevant teachings provided by the instant specification are directed to the creation of the above transgenic mouse but do not support the creation of other transgenic non-human animals encompassed by the claims.

The following aspect of the rejection under 35 U.S.C. 112, first paragraph is directed to claims 5-6 and 38 as they read on the use embryonic stem cells for the creation of transgenic knockout non-human animals:

Both the specification and the state of the art have taught that the transgenic knockout technology requires the use of embryonic stem cells that have been genetically manipulated to comprise a disruption in a nucleotide sequence of interest. The specification has not taught creation of a transgenic knockout non-human animal by methods that do not require embryonic stem cells. Presently, the transgenic knockout technology is limited to the mouse system. See below.

With regard to the claim breadth directed to transgenic non-human animals, the specification fails to teach the production of any transgenic non-human animal comprising a disruption in a TSH-R gene other than a transgenic knockout comprising a disruption in the nucleotide sequence set forth in SEQ ID NO: 1. It is well known in the knockout art that the production of knockout animals other than mice is undeveloped. This is because ES cell technology is generally limited to the mouse system, at present, and that only "putative" ES cells exist for other species. See Moreadith et al. at page 214, Summary. Seamark (Reproductive Fertility and Development, 1994) supports this observation by reporting that totipotency for ES cell technology in many livestock species has not been demonstrated (page 6, Abstract). Likewise, Mullins et al. (Journal of Clinical Investigation, 1996) state that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page S38,

column 1, first paragraph). As the claims are directed to transgenic non-human animals (claims 5-6) or a method of making a transgenic mouse (claim 38), which must be generated by the introduction of a transgene into an ES cell, the state of the art supports that only mouse ES cells were available for use for production of transgenic mice. Finally, claim 38 is appropriately rejected, as the steps of the method require introducing a targeting construct into any cell. Given the unpredictable state of the art it would have required undue experimentation for the skilled artisan to create transgenic knockout non-human animals of species other than the mouse.

Claims 5-6 encompass transgenic non-human animals that comprise a disruption in a TSH-R gene that do not exhibit any particular phenotype. Claims 12-14, 18-22, 25, 28-31, 36 and 40 recite phenotypes that are overly broad and are not supported by the instant specification. Claims 5-6, 12-38 and 40 read on heterozygous and homozygous transgenic non-human animals, particularly mice. The state of the art at the time of filing was such that one of skill could not predict the phenotype of a knockout mouse (See Moreadith et al., 1997, J. Mol. Med., Vol. 75, pages 208-216). In particular, Moreadith et al. discuss that gene targeting at a particular loci is unpredictable with respect to the resulting phenotype since often the generation of knockout mice, in many instances, changes the prevailing notions regarding the functions of the encoded proteins. Moreadith et al. go on to report that gene targeting at the endothelin loci led to the creation of mice with Hirschsprung's disease instead of the anticipated phenotype (abnormal control of blood pressure). See page 208, column 2, 2nd paragraph. Moens et al. (Development, Vol. 119, pages 485-499, 1993) disclose

that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (see abstract). The specification has asserted that the nucleotide sequence set forth in SEQ ID NO: 1 encodes a TSH-R. However, given the state of the art it would be difficult to predict any phenotype resulting from disruption of the sequence of SEQ ID NO: 1. The specification discloses that the phenotypes exhibited by homozygous transgenic knockout mice comprising a disruption in the nucleotide sequence set forth in SEQ ID NO: 1 are as follows: dwarfism; hunched posture; small eyes and ears; small thymus gland; a malformed femur; small skeletal muscle; decreased fat in the subcutis; small or not visible seminal vesicles; low body weight; short body length; low organ weight (spleen, liver, kidneys, heart, thymus); low organ weight to body weight ratio (spleen, liver, kidneys); small thyroid gland with small follicles; abnormalities of the pituitary gland consisting of adenohypophysis, large and vacuolated cells, reduced chromophils, pars distalis, and chromophobe hypertrophy; dysplasia of the epiphyses of the femur, tibia and stifle joint; reduced patchy ossification of bones; reduced cellularity of bone marrow; hypoplasia with absence of cortico-medullary distinction of the thymus gland; immature kidneys with small glomeruli, lymphocytic infiltrates in the kidneys; immature testes; hypospermatogenesis; insterstitial Leydig cell hyperplasia; oligospermia; lymphocytic infiltrates in the lungs; diffuse retinal fibrosis and elevated blood urea nitrogen. See pages 55-62 of the specification. Claims 5-6, as written, do not include a phenotype that differs from a wild-type mouse. Moreover the skilled artisan would know how to use a transgenic knockout

non-human animal that lacks a phenotype, particularly because the instant specification has not provided uses for such; the transgenic mice exhibited the recited above phenotypes may be used for drug testing according to the instant specification. Inclusion of a phenotype associated with a disruption of the nucleotide sequence set forth in SEQ ID NO: 1 in a mouse in the claims would overcome this aspect of the rejection. The specification overcomes the unpredictability in obtaining a phenotype (as discussed above) associated with a homozygous disruption of the nucleotide sequence set forth in SEQ ID NO: 1 in the genome of a transgenic mouse; however, claims 12-14, 18-22, 25, 28-31, 36 and 40 are not commensurate in scope with the enabled phenotype disclosed in the specification. All of the claims recite language that reads on transgenic mice that are homozygous or heterozygous for the disruption. As previously discussed only the transgenic mice whose genomes comprise a homozygous disruption of the nucleotide sequence set forth in SEQ ID NO: 1 exhibit the above discussed phenotypes. Given the unpredictable nature of a phenotype that results from disruption of a nucleotide sequence it would have required undue experimentation for the skilled artisan to make and use the invention as claimed.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the production of transgenic non-human animals comprising a disruption in a TSH-R gene, the lack of direction or guidance provided by the specification for the production of transgenic non-human animals comprising a disruption in a TSH-R gene, the absence of working examples for the demonstration or correlation to the production of a transgenic knockout non-human animal that exhibits a

phenotype other than the exemplified mouse, the unpredictable state of the art with respect to a phenotype that results from disruption of a given nucleotide sequence, the undeveloped art pertaining to the establishment of true embryonic stem (ES) cells of animal species other than mouse, and the breadth of the claims drawn to all non-human animals, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Official Fax Center number is (703) 872-9306.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS
PATENT EXAMINER

Application No.:10/045,624

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [X] 7. Other: **The sequence in Fig. 2A is unidentified.**

Applicant Must Provide:

- [ ] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [ ] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [ ] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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